UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,553	05/02/2002	Audrey Goddard	P3230R1C001-168	9988

20995 7590 01/13/2006

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 01/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,553	GODDARD ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-7,9 and 11-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-7,9 and 11-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/27/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1 – 3, 8, and 10 are canceled. Claims 4 – 7, 9, and 11 – 17 are pending and under examination.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

3. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 27 October 2005 has been entered.

Withdrawn Rejections and Objections

4. The following objections and rejections made in the previous office action are withdrawn:

1) The objection to claims 14 and 15 is withdrawn in light of applicant's amendments.

2) The rejection under 35 USC 112, first paragraph, for containing new matter is withdrawn in light of applicant's amendments.

3) The rejection of claims 14 and 15 under 35 USC 112, first paragraph for not being fully enabled over their scope is withdrawn, only to the extent that it concerns SEQ ID NO:74. This rejection is maintained for other reasons set forth below.

4) The rejection of claims 14 – 17 under 35 USC 112, first paragraph, for lacking written description is withdrawn, only to the extent that it concerns SEQ ID NO:74. This rejection is maintained for other reasons set forth below.

Maintained Rejections and Objections

Priority

5. Applicant asserts, on p. 6 of the remarks, that the instant invention is entitled to benefit of previously-filed applications dating back as far as 25 June 1998. The examiner concedes that the chain of priority recited by applicant is correct. However, as the first disclosure of any results of experiments involving either the claimed protein or a nucleic acid encoding that protein was provided on 24 August 2000, that is deemed the effective filing date for the

purposes of applying prior art. Applicant has not provided any evidence that any of the applications filed before that date do in fact provide the results of the assay reported on p. 140 – 144.

Information Disclosure Statement

6. Applicant asserts that alignments and indications of percentage identity are sufficient identifying information. However there is no indication as to where the sequences were obtained or when they were publicly available. Should applicant desire specific sequences be considered by examiner, the accession numbers and dates of public availability of each accession number, as well as the name of the database in which the sequence can be found, should be submitted on an IDS.

Claim Rejections - 35 USC §§ 101 and 112

7. Claims 4 – 7, 9, and 11 – 17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

This rejection is maintained for the reasons set forth in the previous office actions and reiterated herein. The claims encompass proteins at least 95% identical to SEQ ID NO:48 which is differentially expressed in certain tumors compared to normal controls from the same tissue or is encoded by a nucleic acid which has such expression pattern. The specification discloses that a small undisclosed stretch of SEQ ID NO:47 (about 200 – 600 bp, see p. 140 paragraph 0530), a nucleic acid which encodes to SEQ ID NO:48, is expressed more highly in normal stomach than stomach tumor, and more highly in rectum tumor than in normal rectum. There are no data presented as to whether the protein (SEQ ID NO:48, also called PRO994) is differentially expressed in any tumor, nor is there evidence of the utility of the protein for diagnosis or treatment of any disease. Applicant argues extensively that the disclosure of data on nucleic acids is sufficient to confer utility on the claimed proteins, but provides no evidence as to the over- or under-expression of the protein in any disease or condition, and also provides no evidence that the claimed proteins can be used for treatment or diagnosis.

On pp. 7 – 8 of the remarks filed 27 October 2005, applicant cites *Brenner v. Manson* in support of the argument that the claimed invention has a substantial utility. The selection of the closing lines of the Brenner decision is particularly appropriate to the instant case. Here,

applicant has reported the results of an experiment in which a nucleic acid is differentially expressed in tumors versus normal tissues. The data presented in the specification are the results of experiments on nucleic acid, whereas the claims are drawn to proteins. The specification does not provide evidence that the protein is overexpressed in any disease or condition. The *Brenner* court clearly indicated that the patent system is related to commerce and not philosophy, and that the granting of a patent coincides with the conclusion of a search, not the decision to undertake one. On p. 8 of the remarks, applicant cites MPEP § 2107.01, specifically to argue that any reasonable use identified by applicant should be sufficient to fulfill the "substantial utility" requirement. Here, no reasonable use has been identified for the claimed proteins, as the only data presented are from experiments with nucleic acid.

Applicant also cites MPEP § 2107.01 III, and the text from *In re Brana* cited therein to support the argument that some additional research can be required. The *Brana* case is not analogous to the instant case. Brana et al. had filed an application directed to 5-nitrobenzo [de]isoquinoline-1,3-dione compounds for use as antitumor substances, which differed from several prior art compounds due to the presence of a nitro group at one position on the compound and an amino or other amino group at a different position. In the prior art Paull et al. had disclosed similar compounds that had antitumor activity, and one of the similar compounds from Paull et al. "NSC 308847" had been found to have excellent activity against two specific in vivo murine tumor models. In addition to comparing the effectiveness of the claimed compounds of Brana et al. with that of the antitumor compounds disclosed in Paull et al., the specification of Brana et al. illustrated the cytotoxicity of the structurally similar claimed compounds of Brana et al. against human tumor cells in vitro, and concluded that these tests "had a good action." The Federal Circuit concluded that these tumor models represented a specific disease against which the claimed compounds were alleged to be useful, and that the prior art supported the conclusion that one skilled in the art would be convinced of the applicants' asserted utility, even if some of the compounds were later found not to possess anti-tumor activity in human trials.

The compounds of Brana et al. were asserted to be antitumor agents, which have a specific, substantial and immediately testable activity, which are useful against a specific disease condition. Furthermore there were shown to have similar in vitro activity and were structurally similar to known compounds which had been shown to have the same use. In contrast in the instant case, there are no data, in vitro or in vivo, to support the utility of the claimed products, and there is no comparison with any prior art product of similar structure.

Applicant also cites *Juicy Whip v. Orange Bang* and quotes the text from *Brooktree* cited therein. Applicant's arguments have been fully considered. While the quotation is of course correct, it appears to be divorced from its context. The text appears at the beginning of a discussion as to whether or not products which are intended to deceive, such as cubic zirconium and the juice-dispensing devices which are the subject of the *Juicy* case, can still be "useful" within the scope of § 101. As the claimed products are not intended to deceive, a more detailed discussion of *Juicy* appears not to be germane.

Applicant also cites MPEP § 2107 II(B)(1). When applicant quoted this passage in the previous response, the examiner noted that the text is on point to rejections for lack of credible utility. The instant claims have not been rejected for lack of a credible utility, but rather for lack of specific and substantial utility. Thus this section of MPEP is not on point.

Applicant also cites MPEP § 2107.02 III(A) and (B). The text from section A is directly on point. Applicant has asserted, without providing any evidence, that the claimed antibodies are useful for treatment or diagnosis of disease. This assertion is based on extrapolation of nucleic acid data. The examiner has provided evidence that one of skill in the art *would* have reason to question the truth of the statement of utility and has provided several references which show that the correlation between nucleic acid expression and protein expression is not as high as applicant might hope. Thus the artisan would have reason to question the truth of the statement of utility. The text from section B is again drawn to questions of credible utility. The examiner notes that no rejection for lack of credible utility has been made, and such rejections are properly reserved for wholly incredible assertions, e.g. those that violate the laws of thermodynamics.

On p. 9, applicant cites the same cases that were cited in the previous response. The examiner responded to each and every one before, and since no new facts have been presented the facts in this case are not sufficiently analogous to any of the cited cases. Rather applicant is directed to pp. 5 – 7 of the previous office action for the reasons why the fact patterns of those cases are not analogous to the instant case. While the examiner concedes that statistical certainty is not required for utility, in the instant case there is no evidence that the claimed product is useful as asserted, and there are several references already of record which lead the artisan to doubt the asserted use.

Beginning on p. 13, applicant argues that since the nucleic acid is over-expressed in one tumor and under-expressed in another, the examiner should concede that the antibodies are

useful. Applicant refers again to the first declaration by Dr. Grimaldi, submitted with the previous response. Applicant argues that the PTO must accept the declaration. The examiner set forth several reason why the declaration is not sufficient (see office action mailed 26 July, pp. 7 – 9). Furthermore, the examiner notes that in assessing the weight to be given expert testimony, the examiner may properly consider, among other things, 1) the nature of the fact sought to be established, 2) the strength of any opposing evidence, 3) the interest of the expert in the outcome of the case, and 4) the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993).

Here, there are no data on the claimed invention, no actual data have been submitted, the examiner has cited several articles which constitute opposing evidence and the declarant is also an inventor and thus has a considerable interest in the case. For these reasons, the declaration by Dr. Grimaldi fails to overcome the rejection.

Applicant also cites the articles by Hu and Tokunaga (both of record) and appears to be arguing that certain deficiencies in the methodology are sufficient to overcome applicant's lack of evidence. Applicant's arguments have been fully considered but are not persuasive. Minor technical details aside, Hu and Tokunaga are both quite relevant to the instant case. Hu teaches that nucleic acid expression is not well-correlated with disease, particularly when the expression levels aren't much elevated above baseline. In the instant case, the declaration by Grimaldi indicates that 2-fold expression change, visually determined, was arbitrarily decided to be an appropriate cut-off. However Hu teaches that using 5- or even 10-fold is more appropriate. Tokunaga was cited in support of the examiner's assertion that the utility is not substantial. The article provides evidence that data based on nucleic acid results alone do not impart "ready-to-use" form to other products, and that considerable additional research is needed.

On p. 15 of the remarks, applicant refers to the second declaration by Dr. Grimaldi, submitted with the previous remarks. The examiner notes again that Dr. Grimaldi is an inventor on the instant application and as such is presumed to have a strong interest in the outcome of the case. His opinions, especially in the absence of evidence, are considered with this knowledge in mind. Dr. Polakis is not an inventor of this application, but is an employee of the assignee, Genentech (see declaration by Polakis, paragraph 2). As set forth previously neither

of the two Grimaldi declarations nor the Polakis declaration provide evidence related to the claimed antibodies. Applicant's additional arguments presented in the remarks filed 27 October 2005 fail to compensate for the deficiencies previously noted.

Applicant also refers again to the previously-submitted exhibits 4 – 8. However there is no indication of the relevance to the claimed proteins. The teachings are of a general nature and thus are not deemed to be persuasive for the reasons set forth previously.

Applicant refers again to the declaration by Dr. Ashkenazi submitted previously. Applicant relies on the first declaration of Dr. Grimaldi as establishing that the data from Example 18 are reliable. The examiner has not made the same conclusion for the reasons set forth above. Applicant argues that since Haynes does not teach that there is no correlation between mRNA and protein, the examiner should determine that the claimed proteins are useful. Applicant's arguments have been fully considered but are not persuasive. Haynes was presented as a reference that shows that one of skill in the art would have reason to doubt the assertions made in the specification and declarations. Applicant has not provided any evidence that the claimed proteins are useful as asserted, and the examiner has presented evidence showing one of skill in the art would have reason to doubt the assertions.

On p. 23 of the remarks, applicant cites text by Gygi (reference 27 on IDS filed 2 June 2005). While Gygi teaches that of all the proteins studied, the correlation coefficient between mRNA and protein abundance was 0.935, the data are clearly skewed by the inclusion of a relatively small number of points at the extremes of the data set. When those points are excluded, leaving 69% of the original data set, the correlation coefficient is only 0.356 (see legend of Figure 5), and teaches that for a randomly selected protein the correlation coefficient would be expected to be less than 0.4 (Gygi, p. 1727, bottom of first column). In the instant case, the specification fails to provide evidence of a correlation between mRNA levels and protein levels for the claimed protein. Furthermore the specification does not disclose the number of copies of either mRNA or protein per cell, so there is no way to tell where on Gygi's Figure 5 the levels would fall, and Gygi is not on point to the specific protein that applicant is claiming as his invention.

Applicant also refers to text from Cell 3rd and Cell 4th, as well as Lewin. None of these references are on point to the claimed antibodies or the nucleic acid of SEQ ID NO:47. Applicant also cites Chen (of record). Applicant argues that because Chen did not first select differentially expressed mRNA, the article is not relevant (see remarks p. 25, first paragraph, for

example). Applicant's arguments have been fully considered but are not persuasive. Selecting only those mRNAs which are differentially expressed would put an unreasonable bias into the dataset. The question is not whether certain pre-selected data points show a correlation, but rather whether or not there is such a strong correlation between mRNA and protein expression that the former is a reasonable surrogate for the latter in the absence of any evidence of actual protein expression. Clearly Chen shows that it is not a reasonable surrogate. While applicant argues that Chen shows a correlation when "larger differences" in mRNA are detected, there is no evidence as to how the differences detected by applicant in Example 18 compare to those detected by Chen. It is entirely unclear whether one is to consider the difference small or large.

On p. 28 of the remarks, applicant argues that the *Juicy Whip* case is germane because a single sentence quoted therein supports applicant's arguments. The examiner disagrees. To the extent that the Juicy Whip case sets a standard under § 101, it allows for the utility of inventions based upon deception. The case did not re-set the standard for utility so that the only time a utility rejection could be imposed would be if the invention was "totally incapable of achieving a useful result". Although such text appears in the case, it is in the background section and does not reasonably constitute the basis of the decision. The examiner maintains that since the § 101 rejection was not made based on an intent to deceive, the *Juicy Whip* decision is not relevant.

Applicant also that *In re Langer* is relevant. The examiner disagrees. In *In re Langer*, the court ruled the Patent Office cannot require clinical testing in humans to rebut a *prima facie* case for lack of utility. In the instant case, the Office has not made such a requirement. Furthermore the Langer court ruled that "Assuming that sufficient reason to question the statement of utility and its scope does exist, a rejection for lack of utility under § 101 will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the statement of utility and its scope as found in the specification are true." Here, the examiner has presented sufficient reason to question the statement of utility. In contrast, applicant has not provided suitable proofs, or in fact any evidence, indicating that the statement of utility and its scope as found in the specification are true. Thus to the extent that this part of the *Langer* decision is applicable to the instant case, it appears to support the examiner's position that a § 101 rejection should be upheld.

Applicant argues that *In re Jolles* is relevant, and claims that the examiner asserted that "there is no evidence of a correlation of protein levels with cancer." The examiner's assertion

was not that there is no evidence of any correlation between any protein and mRNA in any cancer sample, but rather that there is no evidence of a correlation between SEQ ID NO:48 and the presence of cancer. Applicant is not claiming a generic protein overexpressed in cancer, but rather a very specific set of proteins, those at least 95% identical to SEQ ID NO:48 which have the expression pattern recited in claim 4, for example. In *Jolles*, the question was whether or not animal models could be considered reasonably predictive of human disease. That is not an issue here. As set forth in the previous office action, the examiner has conceded that the samples are from human tumors; the question of whether animals are predictive is not relevant. Applicant argues that since animal models can be predictive of human physiology, the examiner should conclude that the finding that there is sometimes a correlation between mRNA and protein is sufficient evidence to grant utility to the proteins. The examiner disagrees. Animal models are useful because they allow one to reasonably model the disease *in vivo*, and to test drugs which may have undesirable side effects before administering them to humans. Measuring mRNA levels and protein levels can both be carried out by an artisan of ordinary skill. Measuring protein is not so difficult, toxic, or dangerous that one has to rely on nucleic acid data instead. The animal model analogy does not apply.

Applicant also argues that *In re Irons* is relevant. The examiner disagrees. The fact patterns are very different. In *Irons*, evidence was submitted that indicated that the drug had been administered to 888 patients and that statistically significant results were obtained showing an improvement in arthritic conditions. In the instant case, no such evidence has been submitted. The only data of record are drawn to the nucleic acid, but the instant claims are drawn to antibodies. Furthermore, there is no evidence of record indicating a statistically significant result at the protein level. The claimed protein has never been administered to a human patient, or to an animal, and has never been detected in a cancer tissue sample. It has not been shown to be effective in diagnosis or treatment of anything. The examiner is unable to determine how this is analogous to a case where a drug had actually been administered to patients and shown to induce statistically significant improvement in a disease.

The *Sichert* court ruled that blind comparative studies of the claimed compositions, which showed that the compositions were effective in relieving lymphatic congestion (as narrowly defined), were sufficient to establish utility of said compositions under 35 USC § 101. In the instant case, applicant has not shown any such studies, and therefore because the fact pattern is sufficiently different the *Sichert* case is not germane. Applicant argues that the

Sichert case forms a relevant precedent because a utility which is not wholly incredible should be accepted. However no rejection for lack of credible utility has been imposed by the office, thus this argument is not relevant.

The examiner set forth the reasons that the *Raytheon* case is not relevant in the previous office action. Applicant has responded not by showing where a difference in claim interpretation exists, but rather by arguing that there is a correlation between expression of SEQ ID NO:48 and SEQ ID NO:47, even though data are only disclosed for the latter. This is a) not convincing, as no data on either SEQ ID NO:48 have been presented and b) not relevant, as the *Raytheon* case dealt with claim interpretation, which is not an issue here.

Applicant also argues that *In re Oetiker* is relevant even though no claims stand rejected under 35 USC § 103, as both §§ 101 and 103 require that the office set forth a *prima facie* case. The reasons why a *prima facie* case for lack of utility has been convincingly established are set forth above, and for the sake of brevity will not be reiterated.

Applicant argues that the court's decision in *Fujikawa v. Wattanasin* is relevant. As stated by applicant, the court ruled that test results need not absolutely prove the asserted utility. Applicant also argues that the combination of data presented on a fragment of a nucleic acid encoding SEQ ID NO:48 constitute test results on the claimed product, a group of proteins related to SEQ ID NO:48. The examiner contends that the reported test results are the results of experiments on a different product. The art of record indicates that there is substantial unpredictability in the correlation between the degree of nucleic acid expression and protein expression. Applicant has not presented any data on the degree of expression of SEQ ID NO:48, and has not provided any evidence as to the utility of the claimed proteins. Thus the facts in the instant case simply are not analogous to those in *Fujikawa*. In *Fujikawa*, test results were provided. Here, no test results have been provided, so the question of whether or not the results are sufficient cannot even be entertained.

Applicant also argues that *Cross v. Iizuka* is relevant, even though no test results have been provided. The issue here is the same as that addressed in the previous paragraph. Given the lack of any data, either *in vitro* or *in vivo*, on the claimed protein, one cannot even address the question of whether the *in vitro* tests are sufficiently predictive of *in vivo* physiology. The examiner has set forth the reasons why the *in vitro* data on nucleic acids are not sufficiently predictive of protein expression levels, and applicant has not presented evidence that the claimed proteins are useful.

8. Claims 4 – 7, 9, and 11 – 17 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

9. Even if utility were found for PRO994 (SEQ ID NO:48), enablement would still not be commensurate in scope with claims 4 – 6, 9, 12 – 17 because the specification does not reasonably provide enablement for fragments or variants 95% or 99% identical to SEQ ID NO:48 which are more highly expressed in normal stomach tissue or rectum tumor compared to stomach tumor or normal rectum tissue, or for fragments or variants encoded by polynucleotides with said expression profile, or for the fragments selected from the group consisting of amino acids 32 – 39 and 111 – 190. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 4 – 5 and dependent claims 12 – 13 have been amended to recite that the polypeptide be more highly expressed in normal stomach or rectum tumor tissue than stomach tumor or normal rectum tumor respectively, and the claims further require that the protein be at least 95% (claims 4, 12 – 13) or 99% (claim 5) identical to SEQ ID NO:48. However, the instant specification does not provide any working examples of proteins which meet those limitations. There are no examples of any proteins which are expressed more according to this pattern. The only example of any product with such an expression pattern is a small fragment, 200 – 600 bp long, of SEQ ID NO:47, which is a nucleic acid. The fragment used in the experiments is not disclosed, and there is no indication as to what regions of SEQ ID NO:48 it encodes. A skilled artisan would have to resort to an undue amount of experimentation to make and use the proteins as claimed. The specification does not provide guidance as to which regions of the protein are necessary for the fragments or variants to have the claimed expression pattern. The artisan would first have to identify those regions which are crucial for such an expression pattern in protein, if in fact there is one. Then the artisan would have to make variants, and test those variants for the expression pattern. Because the only data in the specification are drawn to nucleic acid, and there is reason to doubt that changes in expression of a small piece of nucleic acid are informative as to changes in the expression of the protein, and because there are no examples of any proteins which have the expression pattern, such experimentation would be undue.

On p. 34 of the remarks, applicant argues that amended claims are analogous to example 14 of the written description training materials. The examiner disagrees. First, it is important to note that the instant rejection is drawn to enablement, not written description and thus is not on point. This was pointed out to applicant on p. 13 of the previous office action, but applicant continues to argue that the written description examples are to be used in evaluating whether or not a claim is considered enabled over its full scope. Nonetheless, Example 14 of the training materials indicates that if an enzyme which is known to have a particular activity is disclosed, it would be inappropriate to make a rejection over claims to 95% variants having the same activity. Importantly, in the instant case, no activity has been disclosed for the claimed protein SEQ ID NO:48. Applicant has not presented evidence that SEQ ID NO:48 fulfills the expression pattern recited in claims 4 and 5. Therefore since the protein with 100% identity to SEQ ID NO:48 is not disclosed to have an activity (here, an expression pattern), Example 14 is not analogous.

Applicant also argues, beginning at the bottom of page 34 of the remarks, that specifying specific residues (see claim 4, part (b), or claim 9, for example), which were formerly identified as extracellular domains, as amino acid numbers only is sufficient to overcome the rejections. However the specification does not provide evidence that these two fragments are useful for anything. There is no evidence that these fragments are overexpressed or under-expressed in any tumor. There is no evidence that the nucleic acids used in Example 18 encode either of these regions. There is no evidence that these small regions are useful for treatment of any disease.

10. Claims 4 – 5 and 12 – 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Applicant cites *In re Kaslow*, *Vas-Cath, Inc. v. Mahurkar*, and *Union Oil v. Atlantic Richfield* as providing the legal basis for the sufficiency of support under the written description requirement. The examiner agrees that these cases form the legal basis for the requirement.

The *Kaslow* and *Vas-Cath* cases are particularly relevant to this issue. The court's decision in *Kaslow* indicates that one is to look to the specification to determine if the claim is described. The examiner can find support for SEQ ID NO:48 in the specification, but cannot

find disclosure of any other sequences which are at least 95% identical to same that are overexpressed in tumor cells. Thus reading the specification, one of skill in the art would not conclude that applicant was in possession of the broad genera and sub-genera encompassed within claims 4 – 5 and 12 - 17.

Vas-cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-cath*, page 1116).

As discussed previously, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Applicant points the examiner to Example 14 of the written description training materials as providing support for the argument that claims to proteins at least 95% identical to the disclosed sequence with an appropriate functional limitation are deemed to meet the description requirement. However that example is drawn to an enzyme. Enzymes are a sub-genus of proteins; and it is generally known which structures are common to enzymes and thus must be preserved (for instance, an ATP-binding domain must be preserved for a kinase to transfer a phosphate to its substrate). The instantly-disclosed SEQ ID NO:48 is not disclosed as being an enzyme and thus Example 14 is not on point. The specification does not disclose regions within SEQ ID NO:48 which are necessary for the expression patterns recited.

Applicant is directed to the flow chart on p. 9 of the Revised Written Description Interim Guidelines Training Materials, available on the internet at <http://www.uspto.gov/web/offices/pac/writtendesc.pdf>, which is analogous to the instant situation. Claims 4 –5 and 12 – 17 are genus claims. Because the recite percentage identity, the necessarily encompass more than one member of the genus. The specification only discloses a single member of the genus, namely SEQ ID NO:48. Thus neither the art nor the specification discloses a representative number of species falling within the genus. There is not

even identification of any particular portion of the structure at either the nucleic acid or amino acid level that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Applicant argues that since claims 14 and 15 recite the limitation "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody", the claims are adequately described. The examiner disagrees. The limitation is meaningless with respect to the claims. The art recognizes that any six amino acids could be used to make an antibody to the instantly-claimed protein (see Hopp et al. 1981 PNAS 78:3824 - 3828), and applicant has not shown which regions of the protein must be preserved for the proper antibodies to be made. Applicant also refers to Example 16 of the written description training materials. That Example is not on point. In that hypothetical example, the issue was whether a claim to an antibody capable of binding to antigen X is considered adequately described by a disclosure of the protein alone. However, in the instant case antibodies are not being claimed. The question in Example 16 was whether or not the skill in the art was so high with respect to the claimed invention that the disclosure of protein constituted an implicit disclosure of the antibody. Here, the disclosure of a protein sequence is not sufficient to provide a description of the claimed variants.

Conclusion

11. No claim is allowed.

12. This is a continuation of applicant's earlier Application No. 10/063553. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel E. Kolker, Ph.D.
January 3, 2006

SHARON TURNER, PH.D.
PRIMARY EXAMINER
1/4/06